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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,827	11/27/2006	Kamal Mehta	RLL-405US	3209

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Ranbaxy Inc.
Intellectual Property Department
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EXAMINER	
SASAN, ARADHANA	

ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
11/30/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/561,827	MEHTA ET AL.	
	Examiner	Art Unit	
	ARADHANA SASAN	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *19-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/29/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Restriction Response

1. Applicant's election with traverse of Group I (claims 1-18) in the reply filed on September 21, 2009 is acknowledged.

The traversal is on the ground(s) that Tenengauzer et al. (US 2003/0176369 A1) (which was cited in the office action mailed 08/19/09) "fails to teach one skilled in the art to formulate a pharmaceutical composition that prevents the conversion of azithromycin monohydrate into other hydrates, namely azithromycin dihydrate. Tenengauzer does not disclose the hydrate purity of the final compositions produced according to any of the disclosed embodiments, nor does it provide any motivation or teachings to one skilled in the art to modify the embodiments in anyway to prevent such conversion. The technical feature of Tenengauzer is to provide for prevention of chemical degradation directly to the azithromycin molecule, and more specifically to the amine group of azithromycin; it does not address or disclose anywhere in the specification how to reduce, prevent, or eliminate any conversion between different azithromycin hydrates."

This is not persuasive because Tenengauzer teaches azithromycin ethanolate monohydrate as the starting material for all examples (Page 2, Paragraph [0019] and Examples 1-6), thereby anticipating the limitation of azithromycin monohydrate. Instant claim 1 recites a "stable oral composition," and Tenengauzer clearly teaches a composition that resists the degradation of azithromycin (Abstract). Since claim 1 lacks novelty, the technical feature linking the inventions of groups I-III does not constitute a

special technical feature as defined by PCT Rule 13.2 as it does not define a contribution over the prior art.

Applicant's arguments regarding the conversion of azithromycin monohydrate into other hydrates are not commensurate in scope with the instant claims because instant claims contain the transitional phrase "comprising" and do not exclude any other form of azithromycin (such as azithromycin dihydrate). Tenengauzer anticipates the limitations of a stable composition comprising azithromycin monohydrate.

The restriction requirement is still deemed proper and is therefore made FINAL.

2. Claims 19-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

3. Claims 1-18 are included in the prosecution.

Priority

4. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on November 29, 2006 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97 and 1.98. Accordingly, the examiner is considering the information disclosure statement.

See attached copy of PTO-1449.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Banon Pardo et al. (WO 02/10181 A1).

The claimed invention is a stable oral composition of azithromycin comprising: an azithromycin premix comprising azithromycin monohydrate and at least one additive; at least one pharmaceutically accepted excipient; and optionally, at least one taste masking agent.

Banon Pardo teaches a pharmaceutical composition "prepared by combining azithromycin monohydrate of lower hygroscopicity with … at least one pharmaceutically acceptable suitable inert diluent and administering it orally …" (Page 10, lines 1-5).

8. Claims 1-4, 6-12, 14-18 are rejected under 35 U.S.C. 102(e) as being anticipated by Tenengauzer et al. (US 2003/0176369 A1).

Tenengauzer teaches a stabilized azithromycin composition including "an intimate admixture of azithromycin and a stabilizing-effective amount of an antioxidant"

(Page 1, [0009]). The stabilized azithromycin composition is "formulated into pharmaceutical formulations such as conventional dosage forms, including tablets, capsules (e.g., hard and soft gelatin capsules), suspensions, sachets, dragees … tablets may be made … by processes including, e.g., … dry granulation …" (Page 1, [0013]). Azithromycin ethanolate monohydrate is disclosed (Page 2, [0019]). "The pharmaceutical formulations typically contain, in addition to the stabilized azithromycin composition, one or more pharmaceutically acceptable excipients, such as binders, fillers, disintegrants, carriers, lubricants, glidants, flavorants, colorants, buffers, thickening agents, etc. Some excipients can serve multiple functions, for example as both binder and disintegrant" (Page 2, [0029]). Examples of tablet disintegrants are starch, pregelatinized starch, sodium starch glycolate, sodium carboxymethylcellulose, crosslinked sodium carboxymethylcellulose (sodium croscarmellose; crosslinked starch available under the registered trademark Ac-Di-Sol from FMC Corp., Philadelphia, Pa.), microcrystalline cellulose, alginates, gums, surfactants, cross-linked polyvinylpyrrolidone (Page 3, [0031]). Examples of binders include, e.g., acacia, cellulose derivatives (such as methylcellulose and carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose), glucose, dextrose, xylitol, polyvinylpyrrolidone, starch paste, sucrose, sorbitol, pregelatinized starch, gum tragacanth, alginic acids and salts thereof such as sodium alginate, and guar gum (Page 3, [0033]). Flavor oils such as peppermint oils, fruit oils (citrus, lemon, orange, grapefruit, lime, banana etc.) are disclosed (Page 3, [0034]). Fillers and diluents such as anhydrous lactose, sucrose, dextrose, mannitol, starch, microcrystalline

cellulose, and anhydrous dibasic calcium phosphate are disclosed (Page 3, [0035]). Lubricants (including magnesium stearate and sodium lauryl sulfate) are disclosed (Page 3, [0036]). Other excipients such as glidants and coloring agents are disclosed (Page 3, [0037]). Dry granulation of tablet blends is disclosed (Page 3, [0038]). Thickening agents such as xanthan gum, guar gum, locust bean gum, and gum tragacanth are disclosed (Page 4, [0043]). Colloidal silicon dioxide is disclosed as a dispersing agent (Page 4, [0045]). Examples 4 and 5 disclose azithromycin tablet prepared by dry granulation (Page 8, [0090] – [0097]).

Regarding claim 17, the limitation of "… wherein the composition shows an absence of azithromycin dihydrate after storage at room temperature and humidity conditions for a period of at least two months, as determined by using X ray diffraction" is a functional limitation. The structural components of the composition based on claim 1 (since claim 17 is dependent on claim 1) are anticipated by the components and structural arrangement taught by Tenengauzer. Therefore, the absence of azithromycin dihydrate after the specific storage conditions is an intrinsic property of the composition.

Regarding claim 18, the limitation of "… wherein the composition has at least 90% dissolution of azithromycin within 30 minutes when an amount of the composition equivalent to 200mg of azithromycin is tested according to USP-2 dissolution apparatus using 900ml sodium phosphate buffer pH 6.0, 37°C, and paddle speed of 100 rpm" is a functional limitation. The structural components of the composition based on claim 1 (since claim 18 is dependent on claim 1) are anticipated by the components and structural arrangement taught by Tenengauzer. Therefore, the dissolution

characteristics of azithromycin according to specific dissolution conditions are intrinsic properties of the composition.

Therefore, the limitations of claims 1-4, 6-12, 14-18 are anticipated by the teachings of Tenengauzer.

9. Claims 1-4, 6-12, 14-18 are rejected under 35 U.S.C. 102(e) as being anticipated by Johnson et al. (US 2003/0228357 A1).

Johnson teaches dry granulation of azithromycin with at least one excipient (Page 1, [0014]). The azithromycin is "non-dihydrate azithromycin" which means all forms of azithromycin other than form A, which is the dihydrate form (Page 2, [0019]). Azithromycin monohydrate is disclosed (Page 2, [0023] – [0035]) and is blended with pharmaceutically acceptable excipients including binders, diluents, disintegrants, lubricants, fillers, and carriers (Page 3, [0041]). Binders including microcrystalline cellulose, gelatin, sugars (including sucrose, glucose, dextrose and maltodextrin), polyethylene glycol, waxes, natural and synthetic gums, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, and hydroxyethyl cellulose are disclosed (Page 3, [0042]). Diluents or fillers including lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), sucrose, dextrose, mannitol, sorbitol, starch, cellulose (e.g. microcrystalline cellulose; Avicel®), dihydrated or anhydrous dibasic calcium phosphate, calcium carbonate, and calcium sulfate are disclosed (Page 3, [0043] – [0045]). Lubricants including magnesium stearate and sodium lauryl sulfate (Page 3, [0046]), and disintegrants including

crosslinked polyvinylpyrrolidone, sodium starch glycolate and croscarmellose sodium (Page 3, [0047]) are disclosed. The blend is compressed into tablets (Page 3, [0053]) and tablets, sachet or powder for suspension are disclosed as the dosage forms (Page 4, [0058]). Flavors including peppermint and fruit flavors (Page 4, [0061]) and colorants (Page 4, [0062]) are disclosed. Glidants such as colloidal silicon dioxide and talc are disclosed (Page 5, [0070]). Tablets were prepared by dry granulation (Page 5, [0075]). Example 2 discloses dry granulation of azithromycin forms (Page 7, [0111] – [0113]).

Regarding claim 17, the limitation of "… wherein the composition shows an absence of azithromycin dihydrate after storage at room temperature and humidity conditions for a period of at least two months, as determined by using X ray diffraction" is a functional limitation. The structural components of the composition based on claim 1 (since claim 17 is dependent on claim 1) are anticipated by the components and structural arrangement taught by Johnson. Therefore, the absence of azithromycin dihydrate after the specific storage conditions is an intrinsic property of the composition.

Regarding claim 18, the limitation of "… wherein the composition has at least 90% dissolution of azithromycin within 30 minutes when an amount of the composition equivalent to 200mg of azithromycin is tested according to USP-2 dissolution apparatus using 900ml sodium phosphate buffer pH 6.0, 37°C, and paddle speed of 100 rpm" is a functional limitation. The structural components of the composition based on claim 1 (since claim 18 is dependent on claim 1) are anticipated by the components and structural arrangement taught by Johnson. Therefore, the dissolution characteristics of

azithromycin according to specific dissolution conditions are intrinsic properties of the composition.

Therefore, the limitations of claims 1-4, 6-12, 14-18 are anticipated by the teachings of Johnson.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tenengauzer et al. (US 2003/0176369 A1).

The teaching of Tenengauzer is stated above.

Tenengauzer does not expressly teach corn oil as a hydrophobic material.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a stabilized composition comprising azithromycin monohydrate and additives including lubricants and flavor oils, as taught by Tenengauzer, include various hydrophobic materials known in the art such as lipids and vegetable oils in the formulation during the process of routine experimentation, and produce the instant invention.

One of ordinary skill in the art would do this because corn oil is an obvious variant of a hydrophobic material such as a lubricant. One of ordinary skill in the art would find it obvious to use various fatty/lipid/oily materials since the simple substitution of one known element for another to obtain predictable results is obvious. Please see MPEP 2141.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Regarding instant claim 5, the limitation of corn oil would have been an obvious variant over the hydrophobic lubricants disclosed by Tenengauzer (Page 3, [0036]) unless there is evidence of criticality or unexpected results.

12. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tenengauzer et al. (US 2003/0176369 A1) in view of Catania et al. (EP 0 582 396 B1).

The teaching of Tenengauzer is stated above.

Tenengauzer does not expressly teach a sweetening agent comprising one or more of aspartame, saccharin sodium, sucralose, and acesulfame K.

Catania teaches taste masking compositions comprising bitter tasting antibiotics such as azithromycin (Page 2, lines 5-14 and line 34). The azithromycin may be mixed

with excipients including sweeteners, flavorants, binders, stabilizers, plasticizers, pigments, and bulking agents (Page 3, lines 37-40). Artificial intense sweeteners such as aspartame and saccharin along with natural sweeteners such as sucrose, fructose, and glucose are disclosed (Page 3, lines 41-45). Flavorants including fruit flavors and mint flavors are disclosed (Page 3, lines 51-54). Binders (Page 3, lines 56-58), pigments (Page 4, lines 3-10), diluents (Page 4, lines 11-16) are disclosed, along with mixing the azithromycin with these additives (Page 4, lines 20-22).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a stabilized composition comprising azithromycin monohydrate and additives including taste masking sweetening agents, as taught by Tenengauzer, include the taste masking artificial intense sweeteners such as aspartame and saccharin that are used in a composition comprising azithromycin, as suggested by Catania, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because azithromycin is known in the art to have a bitter taste that requires taste masking with sweeteners and flavorants when formulating into oral dosage forms, as evidenced by Catania (Page 1, lines 5-37). Catania teaches that “traditional sweeteners are not effective in masking the bitter flavor of powerfully bitter pharmaceutical agents such as azithromycin” (Page 1, lines 35-37) and that the preferred artificial sweeteners used for masking azithromycin include aspartame and saccharin (Page 3, lines 43-45). It is obvious to use a known technique (taste masking of azithromycin with intense

sweeteners) to improve similar products (oral dosage form of azithromycin) in the same way. Please see MPEP 2141.

Regarding instant claim 13, the limitation of a sweetening agent comprising one or more of aspartame, saccharin sodium, sucralose, and acesulfame K would have been obvious over the aspartame and saccharin disclosed by Catania (Page 3, lines 41-45).

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax, can be reached at 571-272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/
Examiner, Art Unit 1615

/Robert A. Wax/
Supervisory Patent Examiner, Art Unit 1615